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REMARKS

Status of the Application.

Claims 1, 19, 28, 30-31, and 33-50 are pending in the application. Applicants reserve the right to file further continuation applications on any subject matter disclosed in the instant application or on the subject matter of any previously or presently cancelled claim. Claims 1, and 39 have been amended herein. Claims 1, and 39 have been amended to more clearly state the metes and bounds of the claim. Applicants assert new matter has not been introduced by the amendment.

The Invention.

The present invention is directed to a cutinase variant having a substitution in at least one amino acid residue selected from the group consisting of Phe at position 180 and Ile at position 178 of SEQ ID NO:2 wherein the variant has increased polyesterase activity or enhanced thermostability as compared to wild-type *Pseudomonas mendocina* cutinase.

Claims 28 and 30 are objected to as reciting "SEQ ID NO:-2". Applicants have amended the claims to remove the improper sequence identifier. Withdrawal of the objection is respectfully requested.

35 U.S.C. §112, first paragraph.

Claims 1, 19, 31, 34-41, 44 and 46-50 (New matter)

Claims 1, 19, 31, 34-41, 44 and 46-50 stand rejected under 35 USC §112, first paragraph as failing to be described in the specification. Specifically, the Examiner asserts that the specification, claims or drawings as originally filed fail to describe a variant that has a mutation at either position 192 (Claim 1 and claims dependent thereform) or position 194 (Claim 39 and claims dependent therefrom) as having increased polyesterase activity and enhanced thermostability. Emphasis in original; see page 5 of the May 15, 2005 Office Action. Applicant respectfully traverses.

Initially, Applicants once again note that SEQ ID NO:2 contains a leader peptide and is numbered beginning at the initiating methionine. The mature sequence, after cleavage of the leader peptide (14 amino acid residues) begins at the alanine in position 15 (*i.e.*, Ala 15

represents the first residue in the protein). Therefore, Phe 180 in the Claims refers to Phe 194 in Figure 18 and SEQ ID NO:2. Thus, the Examiner may be looking for 194 in the specification but should be looking for 180.

Applicants have amended Claims 1 and 39 to more clearly describe what is considered the invention. The currently pending claim now requires increased polyesterase activity or enhanced thermostability. Support for this can be found, for example, on page 1, lines 20-25. Further support may be found, for example, in Tables 1 and 3 where variants having a substitution at residue 192 show an increased polyesterase activity and both increased polyesterase activity and enhanced thermostability, respectively. Similarly, Tables 1, 2 and 3 provide support for the 194 residue.

Applicants respectfully request withdrawal of the rejection.

Claims 1, 19, 28, 30-31 and 33-50 (Written description)

Claims 1, 19, 28, 30-31 and 33-50 stand rejected under 35 USC §112, first paragraph as allegedly containing subject which was not described in the specification in such a way as to convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant respectfully traverses.

Although Applicants must respectfully disagree with the Examiner's assertion, in order to further their business interests and prosecution of the present application, yet without acquiescing to the Examiner's arguments, Applicants have amended claims 1 and 39 rendering this rejection moot. Withdrawal of the rejection is respectfully requested.

Claims 1, 19, 28, 30-31 and 33-50 (Scope of Enablement)

Claims 1, 19, 28, 30-31 and 33-50 stand rejected under 35 USC §112, first paragraph as failing to be described in the specification. Specifically, the Examiner asserts that the specification does not reasonably provide enablement of all cutinase variants having a substitution corresponding to residues 192, 194, and/or 219 of SEQ ID NO:2. Applicant respectfully traverses.

Applicant must respectfully disagree with the Examiner's argument and rationale that the specification lacks guidance. It is well settled that "[t]he first paragraph of section 112

requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance." *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971). Moreover, "a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 169 USPQ at 369.

Applicants believe the variants disclosed in Tables 1-5 provide more than adequate support for the claimed subject matter. Specifically, Table 5 discloses numerous variants having multiple substitutions that have enhanced activity. Furthermore, the claims require that the variant have enhanced activity or thermostability as compared to the wild-type *Pseudomonas mendocina* cutinase. Applicants have provided assays whereby the person skilled in the art can determine if the variant has enhanced activity or thermostability as compared to the wild-type *Pseudomonas mendocina* cutinase.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 USC 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

35 U.S.C. §112, second paragraph.

Claims 1, 19, 28, 30-31 and 33-50

Claims 1, 19, 28, 30-31 and 33-50 are rejected under 35 USC §112, second paragraph being indefinite. Specifically, the Examiner asserts the recitation of "wild-type *Pseudomonas mendocina* cutinase" or wild-type *P. mendocina* cutinase" renders the claims unclear. Applicants respectfully traverse.

Definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings of the prior art, and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the art at the time the invention was made. *See, e.g., Atmel Corp. v. Information Storage Devices, Inc.*, 198 F.3d 1374, 53 U.S.P.Q.2d 1225 (Fed. Cir. 1999), "it is well-established that the

determination whether a claim is invalid as indefinite 'depends on whether those skilled in the art would understand the scope of the claim when the claim is read in light of the specification.'" quoting *North Am. Vaccine Inc. v. American Cyanamid Co.*, 7 F.3d 1571, 1579 (Fed. Cir. 1993). *See also, Howmedica Osteonics Corp. v. Tranquil Prospects, Ltd.*, 401 F.3d 1367, 1371 (Fed. Cir. 2005), wherein the Federal Circuit overturned an invalidity decision, concluding that "one of ordinary skill in the art would readily ascertain from the written description of the patents that the "transverse sectional dimension" calls for a two-dimensional measurement."

Thus, an important consideration in is whether the terms in a claim adequately define to one skilled in the art the metes and bounds of the claim. Applicants have provided a definition of "wild-type" on page 6, lines 30-31, of the present application, i.e., "a precursor protein from which a variant is derived." The precursor protein can be, as the Examiner correctly notes, that the "definition encompasses not only those proteins that occur 'naturally' but also encompasses mutant and variant proteins that are themselves precursors prior to further mutation." Applicants contemplate that the introduction of mutations may be done in an iterative fashion – see, for example, page 4, lines 1-12. Therefore, Applicants have provided a definition readily understood by the skilled artisan; the claims are definite. Withdrawal of the rejection is respectfully requested.

35 U.S.C. §103.

The Examiner has maintained his rejection of claims 1, 28, 30, 33-39 and 41-50 as allegedly obvious over Poulouse, *et al* (US Patent 5,352,594). Applicant respectfully traverses the rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on

applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

Thus, a *prima facie* case of obviousness requires the Examiner to cite to a combination of references which (a) suggests or motivates one of skill in the art to modify their teachings to yield the claimed invention, (b) discloses the elements of the claimed invention, **and** (c) provides a reasonable expectation of success should the claimed invention be carried out. Failure to establish any one of these requirements precludes a finding of a *prima facie* case of obviousness and, without more, entitles Applicants to withdrawal of the rejection of the claims in issue.[1] Applicants urge that the Examiner has failed to establish at least one of the requirements, i.e., a reasonable expectation of success, as discussed below.

Applicants submit that Poulose *et al.* teach ". . . one would in general use the crystal structure of the enzyme to determine which amino acids are within 15 angstroms of the active site regardless of the primary structure of the enzyme. Where no crystal structure is available, positions in the primary sequence about 6 amino acids on either side of a catalytic amino acid would be within the 15 angstrom requirement." (Poulose *et al.*, at col. 5, lines 50-57). Applicants respectfully submit that as the catalytic triad is composed of Ser126, Asp176, and His206 (*i.e.*, positions 140, 220, and 190 of SEQ ID NO:2), there is no teaching nor suggestion in Poulose *et al.* to modify the amino acid at any of the currently claimed positions in order to increase the polyesterase activity and/or thermostability of the enzyme. The Examiner has acknowledged this assessment (see page 9 of the Office Action).

At best Poulouse *et al.* is an invitation to try. The "obvious to try" standard in determining the patentability is a standard which has been thoroughly discredited. Indeed, an obviousness rejection is inappropriate, where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful." *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988); *Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 10 USPQ2d 1843, 1845 (Fed. Cir. 1989). For example, there is no direction within Poulouse *et al.* as to which, *if any*, amino acid falling within *6 amino acids* on *either* side of *any* one of the *three residues* in the catalytic triad could be

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1 *See e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); and *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

replaced with *any* one of the other *19 amino acids* would result in enhanced thermostability and/or polyesterase activity. There is no motivation to select from the (6*2*3*19=) 684 possibilities provided the currently claimed invention.

Under patent law with regard to obviousness, a reasonable expectation of success is to be assessed from the perspective of one of ordinary skill in the art at the time the invention was made. At the time the invention was made it was well established that altering amino acid sequences could result not only in differences in the expression and secretion levels of the protein but also alter the properties of the protein. It was very likely that altering the amino acids in the catalytic region would result in a decrease in the enzymatic activity or thermostability. This supports Applicants' position that one skilled in the art would not have a reasonable expectation of success in altering the amino acid sequence as presently claimed, e.g., creating the variant I192M, would enhanced thermostability and/or polyesterase activity.

As previously indicated, during the development of the presently claimed invention, Applicants conducted experiments using the best-performing variants as described by Poulose *et al.* (*i.e.*, S205N, Q127S/S205N, and S205N/F207T) to determine their polyesterase activity. The activity of these variants was found to be unremarkable, as compared to the wild-type cutinase. As the teachings of Poulose *et al.* were insufficient to meet the need addressed in the present application (*i.e.*, variants with enhanced thermostability and/or polyesterase activity), the present inventors developed the presently claimed invention in order to provide cutinase mutants with these desired properties. Should the Examiner wish to review these data, Applicants will provide them upon request.

In addition, Applicants submit that Poulose *et al.* teach ". . . one would in general use the crystal structure of the enzyme to determine which amino acids are within 15 angstroms of the active site regardless of the primary structure of the enzyme. Where no crystal structure is available, positions in the primary sequence about 6 amino acids on either side of a catalytic amino acid would be within the 15 angstrom requirement." (Poulose *et al.*, at col. 5, lines 50-57). Applicants respectfully submit that as the catalytic triad is composed of Ser126, Asp176, and His206 (*i.e.*, positions 140, 220, and 190 of SEQ ID NO:2), there is no teaching nor suggestion in Poulose *et al.* to modify the amino acids at any of these positions in order to increase the polyesterase activity and/or thermostability of the enzyme.

Poulose *et al.* teach mutations that increase the perhydrolase:hydrolase ratio. In order to do this you can either increase the numerator or decrease the denominator. In other words, Poulose *et al.* teach mutations that increase the perhydrolase activity of the enzyme or decrease the hydrolase reaction.

As the presently claimed invention is neither taught, suggested, nor is there any expectation of success in producing the presently claimed invention provided in Poulose *et al.*, Applicants respectfully submit that the presently claimed invention is unobvious over Poulose *et al.* Therefore, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In light of the above amendments, as well as the remarks, the Applicants believe the pending claims are in condition for allowance and issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 846-7615.

Respectfully submitted,
GENENCOR INTL., INC.

Victoria L. Boyd

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Victoria L. Boyd
Registration No. 43,510

Genencor International, Inc.
925 Page Mill Road
Palo Alto, CA 94304
Tel: 650-846-7615
Fax: 650-845-6504